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TITLE OF CONTRACT

APPLICATIONS OF ALGEBRAIC AND COMPUTATIONAL TOPOLOGY IN BIOLOGY AND CHEMISTRY

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INTRODUCTION

The United States Office of Naval Research supported this project for a seven year period beginning October 1, 1984. The ground-breaking nature of the research made the initial decision to fund the project a risky one for any granting agency. The original goal of this Florida State University ONR project was to find and develop new and significant applications of mathematics (particularly topology) to science (particularly biology and chemistry). As the project matured and prospered, new goals were set and reached, including research in neural networks. The project was very successful, and now other agencies (including the National Science Foundation) are supporting the ongoing research begun with ONR support. The ONR was willing to support this research at the beginning when no other granting agency was willing to do so.

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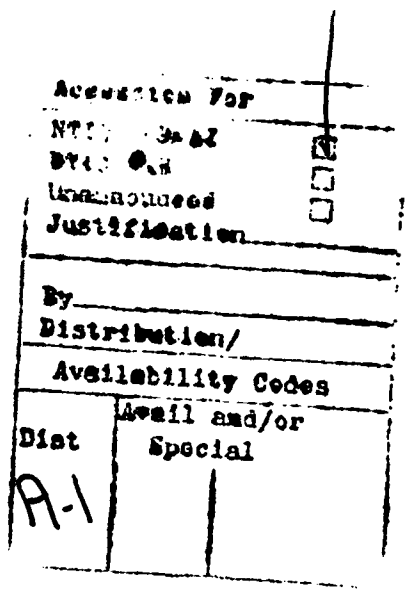

SUMMARY OF WORK ACCOMPLISHED

The following narratives briefly describe the work accomplished on ONR support. The references below are found in the master list of ONR publications.

1. TOPOLOGICAL ENTANGLEMENT IN POLYMERS

This work centers around the fundamental problem of understanding the supermolecular structure of semicrystalline polymer and the applied problem of discovering the relationship between that structure and physical properties of these polymers. Semicrystalline polymer consists of crystal lamellae surrounded by an amorphous region of uncrystallized material. Both the crystallites and the amorphous region consist of molecular subchains of polymer molecules. These crystal and amorphous subchains are several orders of magnitude shorter than the polymer chain molecules constituting the system, and a given polymer molecule may wander in and out of the crystallized portion a number of times, reentering the same crystal (forming a loop) and/or traversing the amorphous region from one crystal to another (forming a tie). The amorphous region is an interstitial fluid of entangled subchains holding the individual crystallites together and thus must ultimately be a key determinant for *macroscopic properties, particularly mechanical properties*, of the material.

The role of amorphous tie subchains has been studied using mathematical models, computer simulation and even some laboratory corroboration due to their single-chain nature. More recently, techniques to simulate, model, and measure the more complex topological chain interactions such as links (formed by two topologically linked loop subchains emanating from distinct crystallites) have been introduced [A3,A4,A8,A12,B3,B8,B9,B19]. In combination with measures of single-chain statistics, these chain- interaction statistics show promise as a tool to understand the material mechanisms and macroscopic mechanical properties of such polymers. The new calculational methods apply within a broad and flexible modelling context to relate chain-interaction statistics to such single-chain statistics as the following:

$$d = \text{exit density} \tag{1}$$

$$d_1, \ldots, d_M = \text{distribution of chain frequencies by reach} \tag{2}$$

$$b = \text{ mean breadth/reach of chains in the model} \tag{3}$$

Here ***exit density*** is the number of amorphous chains exiting a crystal face per unit area; ***reach*** of a chain is the maximum distance it travels away from its face of origination

and *breadth* of a chain is the maximum distance it travels in either direction parallel to the crystal faces; and M denotes the distance between opposing crystal faces. The input parameters given by equations (1)-(3) are characteristics of a given model and may be determined from more elemental model parameters using theory, numerical techniques, or simulation results as the case varies. In the class of walk models, a very fast numerical technique has been devised to calculate (1) and (2) from individual step probabilities. These step probabilities in turn represent the *local isotropy* in the polymeric system so there is reason to hope for methods of estimating them for a given material through experiment. Breadth/reach is a parameter resembling a constrained characteristic ratio.

The most fundamental chain-interaction statistic, *link probability*, derived in [A8], is given for the discrete model case by

$$P_{link}(M) = 1 - d_M - \sum_{i=1}^{M-1} d_i \prod_{j=M-i}^{M-1} [1 - 2b^2 d(i + j + \frac{1}{2} - M)^2 d_j] \qquad (4)$$

The argument for validation of this statistic uses simulation data, curve fitting, and asymptotic analysis.

Two computational models have been developed around these chain- interaction statistics. These "prototype" models have at their core an opposing planes model of the random walk/cubical lattice type in which the individual step probabilities at each lattice site may be specified or determined. From these data the 1- and 2- chain statistics can be computed using a common set of numerical procedures. The models differ in how their input data is transformed into the internal data used for computation.

Model 1 was designed for general investigation of the effect of interphase on amorphous structure[A8]. (Interphase refers to the portion of the amorphous region near the crystallites where the change from order to complete disorder occurs.) More generally, it can be adapted to study virtually all effects of local (an)isotropy as captured in the local step probabilities. The model receives as input the following information: amorphous thickness, interphase thickness, and interphase step probabilities. The thicknesses are expressed in lattice units. From this information various single-chain and chain- interaction statistics are calculated numerically assuming pure isotropy outside the interphase. Using step probabilities generated by the 2-step approximation of Marqusee and Dill to define input for Model 1, their conclusion on the increase in tie probability is confirmed. It is also found that the link-tie ratio remains constant as interphase is added to the model, with the result that increases in link probability are in precise proportion to increases in tie probability. A conclusion is that, in the Marqusee-Dill model, ***the introduction of interphase results in increased levels of both types of amorphous structure.***

Model 2 is really a shell around the first to translate physically measurable parameters of a short-branched copolymer into the internal data required for computation. For specificity, the following discussion concentrates on linear polyethylene with linear alkene branches of between 2 and 10 carbon units and branch probability no larger than 6%.† The model may be visualized as representing a crystalline – amorphous – crystalline portion of the two- phase system using three pairwise adjacent rectangular solids with vertices lying on the standard cubical lattice. The two outer solids represent pure crystalline polyethylene, reflecting the well-established "exclusion principle" whereby short branches on the linear backbone are excluded from crystallite structure by energy considerations. The middle solid represents amorphous (branched) copolymer. The dimensions of these solids in the direction orthogonal to their common faces ("thicknesses") are critical to the behaviour of the model, as are the corresponding thicknesses in real polymer critical to its macroscopic physical properties. The other two dimensions of each solid are assumed large and are therefore not critical. Model input is in terms of the distances W_c = crystal thickness and W_a = amorphous thickness (which must be converted to lattice units n_c and n_a^p, respectively), and p = branch probability. For the crystal portions this conversion is simply W_c divided by bond length and cosine of crystal skew angle for polyethylene, a constant. For the amorphous portion, the conversion factor is a function of the characteristic ratio of the copolymer which is a variable both because it depends on branch probability and because effective branch probability changes in the amorphous region due to the exclusion principle. These conversions specify the "crystal" portion of the model completely. A specification of the "amorphous" portion as an opposing planes model of lattice type is completed by giving a description of the local behavior of amorphous chains in the form of lattice step probabilities. These step probabilities represent the local isotropy of an amorphous chain in the absence of other amorphous chains and will depend on the distance (in lattice units) away from the nearest crystal face. For layers more than one unit away, the probabilities are set for pure isotropy, that is, each of the six directions has probability 1/6. In the layers one unit from the crystal faces, the crystal entry probability is modified by the factor $(1-p)^{n_c}$. This factor represents the probability of finding a sequence of n_c carbon units of pure polyethylene, a condition required for entry into the crystal, assuming Bernoullian distribution of counits in the polymer. The other five step probabilities in these layers are chosen to be equal and so that the sum of all six is unity. This completes an input data set for Model 1 which is then invoked to complete the computation. This is

† The industrial term for these copolymers is "linear low-density polyethylene". Current US production is 4-5 million tons per year.

the first model that takes into account exclusion of both side chains *and* the short linear segments between side chains that are not long enough to extend through the polyethylene crystal.

Calculations have been made using Model 2 for p ranging from 0 to 6% using extrapolations from laboratory data to generate W_c and W_a input [A12,B19]. The results show that sharp maximum values appear in both link and tie probability at around 3% branches and that these probabilities drop below those of unbranched polyethylene at around 5%. These maxima occur at the branch probabilities where radical changes in morphology and mechanical properties begin to occur and constitute evidence of topological linking playing a significant structural role in such materials. *Building into the model the exclusion of side chains and short linear sequences from the crystal structure results in maximal tie and link probability at 3-4% branches.*

Very good and interesting data is currently being produced in the Mandelkern laboratory at Florida State University on the mechanical behaviours of brittle and ductile yield in linear and branched polyethylenes. Alamo, Kennedy, Lacher and Peacock have formed an informal discussion group meeting biweekly in order to gain insight into the mechanistic distinction between brittle and ductile yield in these semicrystalline polymers. Some preliminary calculations using Model 2 have been made with very interesting outcome: *the brittle/ductile transition occurs where the tie and link probability curves cross.*

Prospects for Further Research

Research could be continued in a number of specific directions related to semicrystalline polymers. Long term goals for this research includes better understanding of basic mechanisms determining mechanical properties and the prediction of mechanical properties of hypothetical materials through computer simulation. Through a combination of improvements on current models, improved input for those model, and better understanding of trapped amorphous structure, the problem of prediction of brittleness in hypothetical polymer will be studied. A predictive model, applicable to known as well as hypothetical materials, implemented in software runable on a variety of computers, will be created for investigation of amorphous structure and prediction of the ductility of materials.

2. THE TOPOLOGY OF DNA

One of the first tasks on this project was to survey the area of scientific applications of topology, and then to inform both mathematicians and scientists about the work being done. An overview of the applications in chemistry and biology appears in [A9,B6]. A fundamental question in knot theory and its scientific applications is the number of knots with n crossings [B11]. In [A7] it was proved that the number of prime knots and links grows at least exponentially with crossing number. These growth characteristics are important in the analysis of DNA experiments and in other considerations concerning the influence of topological entanglement on polymer behavior. One area of significant progress on this project is TOPOLOGICAL METHODS IN DNA ENZYMOLOGY. In the topological approach to enzymology, an enzyme extracted from living cells is reacted *in vitro* with artificial circular DNA molecules produced by cloning techiniques. An enzyme reaction produces a topological signature in the form of DNA knots and links. These reaction products are fractionated by gel electrophoresis and the product molecules are coated with *RecA* protein to enhance resolution of the topological structure in electron micrographs. The twisted topology of these reaction products is then mathematically analyzed in order to determine the 3-dimensional structure of active enzyme-DNA complexes, and the changes in DNA topology effected by enzymes in order to mediate the vital life processes of replication, transcription and recombination [A5,A9,B5,B6]. The *tangle model* for the analysis of laboratory enzymology experiments on circular DNA was developed and used to analyze the results of recombination enzymes and topoisomerases. The tangle model provides mathematical proof of enzyme-DNA complex structure and enzyme mechanims, and the algorithmic calculation of that structure. It gives a mathematical framework in which to test biological hypotheses and find hidden biological assumptions. It provides a tool for the wet-lab biologist to use in the analysis of experiments. The tangle model also helps to solve a number of the practical problems faced by biologists using this line of experimentation:

(i) The product of a reaction is a family of DNA knots and links: which product occurs at which stage of the reaction?

(ii) How many products are needed to uniquely characterize the enzyme mechanism?

(iii) Electron microscopy is hard to do and takes a lot of DNA product: gel electrophoresis provides a rough product structure analysis, and can be done with very little product. What is the best experimental mix of the exact information of micrographs with the inexact information of gel electrophoresis in order to analyze a given experi-

ment? Details on the tangle model and the applications to enzymology are contained in [A14,A16,B13,C2]. The topological approach to enzymology and topological considerations in polymers give rise to a number of unsolved mathematical problems; some of these are outlined in [B12].

3. RANDOM KNOTS

Another area of significant progress has been *RANDOM KNOTS AND POLYMERS.* Polymer configuration in dilute solution can be modelled by means of self-avoiding walks on a lattice, the lattice spacing serving to simulate volume exclusion phenomena. Topological entanglement (knotting and linking) restricts the number of configurations available to a macromolecule, and thus is a measure of configurational entropy. A ring polymer can be modelled as a self- avoiding polygon on the lattice. One can think of generating random ring polymers by performing a cyclization (random closing) reaction on a dilute family of linear polymers of the same length N. If one were to perform this reaction, the mathematical problem generated is to describe the yield of such a reaction: what will the distribution of knots and links be from a random closing reaction on a solution of linear polymers, as a function of the length N and the concentration C? A long-standing conjecture in this area was the *Frisch-Wasserman- Delbruck Conjecture*:

FWD CONJECTURE: *The probability that a randomly embedded ring polymer is knotted goes to one as the length N goes to infinity.*

In [A13] a solution of the FWD conjecture was given, proving that, for large N, all but exponentially few self-avoiding polygons of length N on the simple cubic lattice in 3-space are knotted; equivalently, the knot probability approaches one exponentially rapidly. In [A18] the problem of detecting tight knots in a self- avoiding walk is considered. In [A17,B25] the average characteristics of random knots are considered, and it is proved that the embedding complexity goes to infinity at least linearly with the length of the curve. In [A26] the complexity of randomly embedded graphs in the simple cubic lattice is considered, and there it is proved that many measures of entanglement complexity (crossing number, unknotting number, genus, span of a knot polynomial, etc.) increase at least linearly with the length.

In modelling the amorphous region of semicrystalline polymers, one can study the entanglement statistics of random walks on the simple cubic lattice emanating from opposing parallel planes. In [A4] the linking statistics of a Monte Carlo simulation suggest that homological linking of polymer strands in the amorphous region is an important factor in the macroscopic physical properties of the polymer. In [B20,B26], algorithms, data structures

and topological properties of random walks on the simple cubic lattice are derived, and it is shown that four times the writhe of any simple closed curve on the simple cubic lattice is an integer.

4. SPIRAL WAVES IN EXCITABLE MEDIA

Rotating sprial wave patterns in two dimensions are a spatial signature of oscillating chemical reactions (the Belusov-Zhabotinsky reaction, cAMP pulses in slime mold), and are believed to be involved in heart fibrillation and neural seizures. These spiral waves rotate around rotor points, and these points are organizing centers for the wave pattern. The three- dimensional analogue of these spiral waves are scroll waves which rotate around organizing centers which are framed oriented links in 3-space; spiral waves are cross-sections of scroll waves. The wave front is a generalized Seifert surface for the organizing center. A mathematical characterization of these wave patterns and their time evolution in terms of phase maps and homotopy of phase maps was produced. Necessary and sufficient conditions for the existence of a wave pattern (in terms of the characteristics of the pattern near the organizing centers) was derived in both two and three dimensions [B5].

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1. R.C. Lacher, *Computers In The Curriculum*, A report prepared for William D. Law, Jr., Vice President for Institutional and Program Planning, St. Petersburg Junior College, St. Petersburg, FL, 1985.

2. C. Braswell, *Optical mark recognition and data resolution*, MSc Thesis, Florida State University, 1987.

3. C. Ernst, *On knots and tangles*, PhD Thesis, Florida State University, 1988.

4. R.C. Lacher, *The CROSSWALK Simulation: Design, Development, Verification, Analysis, and Data*, ONR Report Number XX xxx- xxx, Discrete Mathematics Research Program, Office of Naval Research, Arlington, VA xxxxx, 1989.

5. *Software Engineering: The Applied Science of Computing* (with R. Salley), White paper on the Florida software industry and the need for cooperative university-industry programs in software engineering education, Department of Computer Science, Florida State University, 1989.

6. K. McCroan, *Displaying geographic information: efficient methods for raster displays*, PhD Thesis, Florida State University, 1990.

7. *Expert Networks: A Neural Network Connection to Symbolic Reasoining Systems* (with S.I. Hruska and D.C. Kuncicky), FSUCS Technical Report 90-092, September 1990.

D. Software Products.

1. CROSSWALK (1985-87). A simulation of extramolecular configuration in crystalline polymers, called state-of-the-art by DOE reviewers. Instrumental in 5 publications and 6 invited lectures. Supported by the US Office of Naval Research.

2. PolyStruct (1987-90). A PC-based suite for calculating various physical and topological structural variables for prediction of material properties of crystalline polymers. Supported by the US Office of Naval Research.

3. KNODES (1988-89). A suite of workstation software for use by scientists and engineers working on reactive flow problems numerically. The modules replace human assistants for many tasks related to the use of large mainframes (supercomputers) for numerically intensive investigations. Supported by the Florida High Technology and Industry Council (design/prototype).

4. ENBP (1991-2). Expert Network BackPropagation learning with influence factors. Portable C version developed with S.I. Hriska. CM FORTRAN version developed with S.I. Hruska and L. Nguyen. Supported by the Florida High Technology and Industry Council.

E. Patents.

1. Patent pending on the machine learning process built around translation and ENBP

algorithm (see FSUCS Technical Report 90-092). Approved 12-90 by FSU Patent Committee. Filed 1-92. Co-holders are R.C. Lacher, D.C. Kuncicky, S.I. Hruska, and Florida State University.

RESEARCH MEETINGS ORGANIZED

The principal investigators organized or helped to organize the following research conferences:

1. *Southeastern Topology Conference*, Tallahassee, March, 1985.
2. *Symposium on Mathematical Chemistry*, Tallahassee, March, 1985.
3. *MATH/CHEM/COMP Research Conference*, Dubrovnik, June 1986.
4. *MATH/CHEM/COMP* Research Conference, Dubrovnik, June 1987.
5. *Mathematical Approaches to DNA Conference*, Santa Fe, January, 1990.
6. MAA Short Course on *Knot Theory and DNA*, MAA Northwestern Section, Portland, June, 1990.
7. Minisymposium on *The Geometry and Topology of DNA*, SIAM National Meeting, Chicago, July, 1990.
8. Technical Session on *New Interactions Between Topology and Science*, AAAS National Meeting, Washington, DC, February, 1991
9. *MATH/CHEM/COMP* Research Conference, Dubrovnik, June 1991.

LECTURING ACTIVITY

During the period of ONR support, the principal investigators were heavily involved in giving invited lectures on these new applications of topology at various departmental colloquia and research conferences. During the period of ONR support, more than 130 research presentations were given.

GRADUATE STUDENTS SUPPORTED

1. Clint Braswell received his MSc degree in April, 1987.
2. Claus Ernst received his PhD degree in August, 198l. Ernst is currently an Assistant Professor of Mathematics at Western Kentucky University, Bowling Green, Kentucky.
3. Keith McCroan received his PhD in August, 1990. McCroan is currently with the Environmental Protection Agency in Montgomery, Alabama.